V THE AUTONOMIC NERVOUS SYSTEM

CANNON OF HARVARD

William Bradford Cannon was born in 1871 in Prairie du Chien, Wisconsin, the site of Fort Crawford, where William Beaumont conducted classic experiments on digestion. Cannon would distinguish himself as a physiologist of Beaumont's rank. Although he was founder of the gastrointestinal roentgen examination and maintained an interest in gastroenterology throughout his life, Cannon's most productive years were spent in the study of the autonomic nervous system and homeostasis. He graduated from Harvard University in 1896 and Harvard Medical School in 1900; he was an instructor in physiology until 1902 and an assistant professor until 1906. From 1906 to 1942, he was George Higginson Professor of Physiology, retiring as Professor Emeritus until his death in 1945.

Apart from his contributions to physiology, Cannon introduced the case method of teaching medicine, later championed by Richard Cabot. Wrote Cannon:

> *When I was a medical student in the late nineties it was customary for us to be subjected to four hours of continuous lecturing, from two until six o'clock five days of every week, mainly on subjects concerned with human beings, their diseases, the means of diagnosing the diseases, and the proper modes of treatment. At that time my roommate was a law student, Harry A. Bigelow, later Dean of the Law School at the University of Chicago. I could not help noting the eagerness and zest with which he and his fellow students discussed cases and their implications and comparing this with the dreary and benumbing process we medical students endured as we filled our notebooks. In my senior year in the Medical School I wrote an article which was published in* The Boston Medical and Surgical Journal *under the title, "The Case System of Teaching Systematic Medicine." The idea of using printed clinical records, that I suggested as a basis for discussing diagnosis and proper treatment, was at once favorably received and put to*

use. Case books on diseases of the nervous system, on general medicine, and on diseases of children soon appeared. Many of the hours which had formerly dragged in mere passive recording in notebooks what the professor recited—often from another notebook!—now sped away in a lively exchange of views among the students themselves and with their instructors. That reform started about 1900. (1945)

During his medical school years, Cannon also published two classic papers on gastrointestinal movements observed for the first time by x-rays. These early studies led to his interest in the autonomic nervous system. In 1896 Professor Henry P. Bowditch urged Cannon, then a freshman medical student, to utilize the newly discovered roentgen ray to study digestion in animals. Cannon fed a goose a bolus of food mixed with bismuth, opaque to x-rays, and recorded a transit time of 12 seconds down the esophagus, demonstrating constant movement characteristic of peristaltic motion (Cannon and Moser, 1898). This initial experiment led to further studies on the motility of the esophagus, stomach, and intestines, but Cannon encountered occasional difficulty interpreting the peristaltic behavior of the animals:

In some animals the peristalsis was perfectly evident and in others there was no sign of activity. Several weeks passed before I discovered that this was associated with a difference in sex: the male cats were restive and excited on being fastened to the holder; the female cats, especially if elderly, submitted with calmness to the restraint, and in them peristaltic waves took their normal course. (1909)

These passive observations led to experiments demonstrating that "the stomach movements are inhibited whenever the cat shows signs of anxiety, rage, or distress." Cannon then focused on the vagus and splanchnic nerves to determine which inhibited peristalsis. His experiments were simple and described in his book *The Mechanical Factors of Digestion,* from which the following is quoted:

. . . When the vagus nerves were severed, and the splanchnic nerves alone remained, respiratory distress caused total cessation of the movements of the stomach and small intestine. Impulses along the splanchnic nerves, therefore, physiologically inhibit not only the intestine, but the stomach as well. When the splanchnic nerves were cut and the vagi alone remained, respiratory distress had no effect upon the small intestine. (1911)

Cannon then demonstrated that epinephrine causes relaxation of the entire gastrointestinal tract, except at the pyloric, ileocolic, and internal anal sphincters.

For 35 years Cannon studied the sympathetic nervous system, arriving at several generalizations. He described the emergency, "fight or flight" response. He introduced the law of denervation, the supersensitivity of denervated structures. He also attributed to the sympathetic nervous system a major role in homeostasis. Author of eight books, his *Bodily Changes in Pain, Hunger, Fear and Rage* (1915), and *The Wisdom of the Body* (1932) present his views on the sympathetic nervous system and homeostasis, respectively. His last book, *The Way of an Investigator* (1945), published the year of his death, is rich in medical history, autobiography, and the philosophy that guided his eminent life.

—CHARLES STEWART ROBERTS

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75 An Overview of the Autonomic Nervous System

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The autonomic nervous system consists of a somatic afferent pathway, a central nervous system integrating complex (brain and spinal cord), and two efferent limbs, the sympathetic and the parasympathetic nervous systems. Norepinephrine is the primary chemical neurotransmitter at sympathetic nerve endings, whereas acetylcholine is the primary chemical neurotransmitter at parasympathetic nerve endings. Acetylcholine, monamines (dopamine, etc.) and several other peptides further modulate the system centrally in the brainstem and hypothalamus.

Since the autonomic nervous system innervates all organs of the body, autonomic neuropathy is a multisystem disorder. Nevertheless, lesions tend to occur in either the afferent, central, or efferent pathways, leading to clinical findings that relate directly to the function of specific autonomic fibers.

History

Table 75.1 lists items of the history that are often abnormal in patients with autonomic dysfunction or sleep disturbances. The most common, by far, is orthostatic hypotension: dizziness or syncope on changing from the supine or sitting to the standing position. This occurs because of a marked reduction in the standing blood pressure, often unaccompanied by the usual compensatory increase in heart rate, because of the autonomic neuropathy.

Diabetic patients tend to develop parasympathetic autonomic neuropathy earlier than sympathetic autonomic neuropathy. Symptoms related to parasympathetic denervation of the bowel and bladder are often prominent. This contrasts with progressive autonomic failure, Shy–Drager syndrome, Riley–Day syndrome, and most drug-induced dysautonomias where the major involvement is sympathetic rather than parasympathetic.

Both sympathetic and parasympathetic autonomic fibers contribute to the arousal, erection and ejaculatory responses in sexual function. Hence, impotence is a relatively early symptom in most dysautonomias.

Physical Examination

Table 75.2 provides a list of the instruments needed for routine and specialized testing of the autonomic nervous system. A watch with a second hand is needed to record heart rates in different positions and to assure at least 7 and preferably 15 seconds' duration of forced expiration during the Valsalva maneuver. An ECG is needed to measure the heart rate responses during the Valsalva maneuver (i.e., ratio of the longest R–R interval post-Valsalva to the shortest R–R interval during the Valsalva).

An ECG is also needed to evaluate the parasympathetic (vagal) mediated changes in heart rate (sinus arrhythmia)

Table 75.1
Symptoms of Autonomic Dysfunction and Sleep Disorders

Symptom	Possible disorder(s)	Chapter(s)
Orthostatic dizziness or syncope	Progressive autonomic failure Shy–Drager syndrome Riley–Day syndrome Drug-induced autonomic dysfunction Autonomic dysfunction in patients with diabetes, alcoholism, Parkinson's disease, etc.	76, 78, 79
Bladder incontinence, nocturia, frequency, loss of sensation of morning fullness, retrograde ejaculation	Autonomic bladder dysfunction	76, 79
Nocturnal diarrhea, fecal incontinence, nausea/vomiting	Autonomic bowel dysfunction	76
Impotence	Organic versus inorganic impotence	76, 79
Gustatory sweating	Diabetic autonomic neuropathy	78
Insomnia	Situational psychophysiological insomnia Sleep apnea Restless legs syndrome Nocturnal myoclonus	77
Nightmares, sleep terrors Sleepwalking Teeth grinding	Parasomnias Somnambulism Bruxism	77
Hypersomnolence	Depression Narcolepsy Cataplexy	77

Table 75.2
Instruments Used to Test the Autonomic Nervous System

Routine clinical tests	Special clinical tests
Sphygmomanometer	Sleep laboratory[a]
Stethoscope	Hand dynamometer
ECG machine	Sweat testing materials[b]
Watch	Bladder function tests
Penlight	Metacholine, homatropine, 1% hydroxyamphetamine and 4% cocaine eye drops
Reflex hammer	
Tuning fork (128 Hz)	GI function tests

[a]For polysomnography, often including an electroencephalogram (EEG), electrooculogram, electromyogram (for facial muscle activity), and equipment for studies of nocturnal penile tumescence.
[b]Can include quinizarin powder, cobalt chloride solution, or starch and iodine materials; 0.01% pilocarpine for intradermal injection.

during quiet deep breathing at a rate of six breaths per minute. The maximum heart rate during inspiration and the minimum heart rate during expiration are calculated for each breath and the test result is the mean of the difference for each of six breaths. Variation of 15 beats/minute or more is normal; variation of 11 to 14 beats/minute is borderline; and variation of less than 10 beats/minute is abnormal.

The reflex hammer and tuning fork are necessary for the evaluation of peripheral neuropathy, which is often present in patients who have autonomic neuropathy, especially diabetics and alcoholics.

Table 75.3 lists the signs of autonomic dysfunction that may be detected on physical examination. The hallmark of all dysautonomias is orthostatic hypotension. When orthostatic hypotension is suggested by the patient's history of dizziness or syncope upon standing, it must be documented by the physical examination. Be careful in measuring the standing blood pressure in such patients because the maximal decrease in blood pressure often occurs within the first 30 seconds, and the patient can slump to the floor with little or no measurable blood pressure until restabilized in the supine position. Have someone assist with the blood pressure and heart rate measurements in patients who are suspected of having severe orthostatic hypotension.

The pupil is an interesting example of a structure with reciprocal innervation from both sympathetic dilator and parasympathetic constrictor autonomic fibers. Adie's pupil is the classic example of parasympathetic denervation, whereas Horner's syndrome is the classic example of sympathetic denervation.

Table 75.3
Signs of Autonomic Dysfunction

Sign	Possible disorder(s)	Chapter(s)
Standing systolic blood pressure decrease ≥20 mm Hg	Progressive autonomic failure Shy–Drager syndrome	76, 78, 79
Standing heart rate increase <10 beats/min	Riley–Day syndrome[a] Drug-induced autonomic dysfunction Autonomic dysfunction in patients with diabetes, alcoholism, Parkinson's disease, etc.	
Unilateral pupil abnormalities:		
Dilated and poorly responsive	Adie's pupil	78, 79
Constricted with ptosis of lid and ipsilateral decrease in facial sweating	Horner's syndrome	78, 79
Rectal sphincter tone decreased	Autonomic bowel dysfunction	76

[a]Often associated with hyporeflexia, absent tears and wide-based gait.